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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/535,814	03/28/2000	Yuh-Jiuan Lin	64,600-024 CIP	5514

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EXAMINER	
BRANNOCK, MICHAEL T	
ART UNIT	PAPER NUMBER
1646	23

DATE MAILED: 07/01/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/535,814	Applicant(s) Lin et al.
	Examiner Michael Brannock	Art Unit 1646

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Sep 11, 2002* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☒ The specification is objected to by the Examiner.

10) ☒ The drawing(s) filed on *Mar 28, 2000* is/are a) ☐ accepted or b) ☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Status of Application: Claims and Amendments

1. Claim 1 is pending.

Sequence Rules Compliance

2. Applicant is notified that the Computer Readable Form (CRF) and the paper copy of the Raw Sequence Listing, presented as Paper 20, 9/12/02, are compliant with the requirements of 37 C.R.F § CFR 1.821 through 1.825 regarding Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. However, there appears to be a discrepancy between the information provided in the Raw Sequence Listings and Figure 4, e.g. the protein (P30955) is listed as having 313 amino acids in the raw sequence listing, whereas Figure 4 indicates that the protein has 330 amino acids. As the protein known as P30955 is known in the art to have 313 amino acids (and is also depicted in Figure 4 as having 313 amino acids) correction of Figure 4 to recite 313 amino acids would be viewed as correction of an obvious clerical error and would not constitute new matter. Appropriate correction/clarification is required. Additionally, Applicant is requested, in response to this Office action, to cancel the previous Paper copies of the Raw Sequence Listing, presented as Paper 6 (9/6/01), Paper 12 (3/11/02), and Paper 18 (7/25/02).

Drawings

3. The drawings are objected to as set forth in the attached PTO-948. A proposed drawing correction or corrected drawings are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

Specification

4. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code, see Figure 4 and page 4, for example. Applicant is required to delete the embedded hyperlinks and/or other form of browser-executable code. See MPEP § 608.01.

Priority

5. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

The second application must be an application for a patent for an invention which is also disclosed in the first application (the parent or provisional application); the disclosure of the invention in the parent application and in the second application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The specification of the parent Application, 09/057,181 does not provide and enabling basis for the invention claimed in the instant Application. The disclosure of the 09/057,181 application does not teach how to practice any embodiment of the invention. No structural information is provided to aid the artisan in constructing the instantly claimed biosensor. The only representation of a receptor provided, the cartoon structure in Fig. 1 of 09/057,181, does not represent the detail or the interaction which would permit the skilled artisan to understand or predict any interaction with any ligand. As is appreciated in the art, the acquisition of structural information regarding receptors whether in the form of sequence data, three-dimensional crystallographic structures, or otherwise, requires extensive labor which is not of a routine nature in the study of integral membrane receptors - and the results of any experiment cannot be predicted merely because the receptor is at hand. The disclosure of the 09/057,181 application sets forth a research plan, not an invention ready to be practiced. The teaching of the 09/057,181 disclosure that an artisan could, for example, obtain a receptor sequence, make various prediction regarding it's structure using various algorithms known in the art, and deduce the therefrom by unspecified means some possible sites of ligand interaction fails to teach the artisan how to actually practice the invention. "Tossing out the mere germ of an idea does not constitute enabling disclosure... [R]easonable detail must be provided in order to enable members of the public to understand and carry out the invention." Genentech, Inc. v. Novo Nordisk Inc., 108 F.3d 1361, 1366, 42 U.S.P.Q.2d 1001, 1005 (Fed. Cir. 1997). Such reasonable detail is lacking in the 09/057,181 application. As was appreciated in the art, the development of any physical or

conceptual model system requires considerable effort, creativity, insight, intuition and a good deal of experimentation. The 09/057,181 application merely provides the skilled artisan with an invitation to gather such effort, creativity, insight, intuition and good deal of experimentation, and, as such, does not meet the requirements of the first paragraph of 35 U.S.C. 112.

Claim Rejections - 35 USC § 112

6.The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claim requires a method for making a biosensor capable of detecting a molecule wherein the molecule is a ligand for an olfactory receptor protein. As it is commonly understood in the art of olfactory receptor proteins, the term "ligand for an olfactory receptor protein" is thought to refer to a molecule that binds to the olfactory receptor protein wherein the binding is capable of promoting the molecular rearrangements in the receptor that are required for the successful activation of G-protein, i.e. the ligand is understood to effect signal transduction. A molecule that could block that interaction (antagonist) is also commonly referred to as a ligand -

as well as are other molecules that promote signal transduction allosterically (agonists). However, the term "ligand" as it is used more generally in the art of biochemistry is thought to refer to any molecule that binds to a macromolecule, irrespective of any functional effects. Such distinctions clearly impact on the bounds of the claimed invention. However, the instant specification and the claims do not set forth a clear definition of the term "ligand for an olfactory receptor protein" such that the artisan could unambiguously know whether or not he or she was practicing the claimed invention.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claim 1 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of making a biosensor comprising attaching the peptide DPDQRDC to a traducer, does not reasonably provide enablement for methods involving any other peptide and nor for the broadly claimed method of making a biosensor cable of detecting a molecule wherein the molecule is a ligand for an olfactory receptor. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification teaches that the peptide DPDQRDC binds trimethylamine with high affinity (e.g. Fig. 5). And that this peptide was discovered through a process of molecular

modeling involving comparisons of a canine olfactory receptor protein with other known GPCRs and further computational methods to deduce possible ligand binding domains. This was followed by testing the various putative ligand binding peptides in an in vitro assay (pages 3-7). The specification, however, provides no specific details regarding the discovery of other ligand binding peptides and merely invites the skilled artisan to try to find them using the very generalized teaching in the specification. There appears to be no specific teaching as to how to find other peptides based on anything more than computational modeling followed by trial and error experimentation.

The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex (see Bowie et al., 1990, Science 247:1306-1310, especially p.1306, column 2, paragraph 2; Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure, pp 492-495, Birkhauser, Boston). However, Applicant has provided little or no guidance beyond the mere invitation to use available analytical programs to try and find other ligand binding peptides. Although the specification outlines art-recognized procedures for producing and screening for active proteins, this is not adequate guidance as to the nature of active proteins that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be

active, which conformation is dependent upon surrounding residues; therefore deletion of the remaining non-essential residues can often destroy activity.

As is appreciated in the art, the acquisition of structural information regarding receptors whether in the form of sequence data, three-dimensional crystallographic structures, or otherwise, requires extensive labor which is not of a routine nature in the study of integral membrane receptors - and the results of any experiment cannot be predicted merely because the receptor is at hand. The instant application sets forth a research plan, not an invention ready to be practiced. The teaching that an artisan could, for example, obtain a receptor sequence, make various prediction regarding it's structure using various algorithms known in the art, and deduce the therefrom by unspecified means some possible sites of ligand interaction fails to teach the artisan how to actually practice the invention. "Tossing out the mere germ of an idea does not constitute enabling disclosure... [R]easonable detail must be provided in order to enable members of the public to understand and carry out the invention." Genentech, Inc. v. Novo Nordisk Inc., 108 F.3d 1361, 1366, 42 U.S.P.Q.2d 1001, 1005 (Fed. Cir. 1997). Such reasonable detail is lacking in the instant application. As was appreciated in the art, the development of any physical or conceptual model system requires considerable effort, creativity, insight, intuition and a good deal of experimentation. The instant application merely provides the skilled artisan with an invitation to gather such effort, creativity, insight, intuition and good deal of experimentation, and, as such, does not meet the requirements of the first paragraph of 35 U.S.C. 112.

Additionally, as pointed out above regarding the second paragraph of 35 U.S.C. 112, the claims, whether intended or not, encompass methods that require that the biosensor utilize a peptide capable of binding "a ligand of an olfactory receptor protein" which includes those ligands that endogenously activate the receptor. The specification has provided no guidance as to how to find such peptides. It is even unclear whether or not trimethylamine is a true ligand of the dog receptor used in example 1. The art recognizes the difficult problem of pairing ligands with olfactory receptors. In fact, Zhao et al. Science 279(237-242)1998 teach that although the odorant receptors may signal through a common motif, the putative odorant receptors constitute the largest subfamily of GPCRs, and in some ways remain the most enigmatic, because no particular mammalian receptor has been definitively paired with any ligand (see page 237, col 1).

Thus, due to the large quantity of experimentation necessary to generate the infinite number of peptides required by the claims and then to screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples other than the single disclosed peptide, the complex nature of the invention, the state of the prior art which establishes the unpredictability of matching ligands based on sequence data and modeled protein structure, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed. invention in its full scope.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

11. Claim 1 is rejected under 35 U.S.C. 102(a) as being clearly anticipated by Wu, T-Z et al., Journal of Biotechnology 80(63-73), July 15, 2000.

Wu et al. disclose a method of making a biosensor capable of detecting a ligand for an olfactory receptor (trimethylamine), comprising determining the amino acid sequence of an olfactory receptor and comparing that sequence to other GPCRs and using the predictions of 2nd

and 3rd structure to determine likely ligand binding domains and synthesizing the peptide and then attaching the peptide to the surface of a transducer, see the text beginning at col 1 of page 64 continuing to col. 2 of page 66.

12. Claim 1 is rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No: 6,218,507.

U.S. Patent No: 6,218,507 disclose a method of making a biosensor capable of detecting a ligand for an olfactory receptor (trimethylamine) comprising determining the amino acid sequence of an olfactory receptor (col 1, L52-64). Further, given the broadest reasonable interpretation of the claim, an ordinary artisan would appreciate from the discussion at col 1, L52-64, that the sequence of the odorant receptor was compared to that of other GPCRs with regard to predictions of 2nd and 3rd structure to determine likely ligand binding domains. The peptide fragments were screened for ligand binding (col 3, L37), and then attached the surface of a transducer (e.g. col 5, L4).

Conclusion

No claim is allowable.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Brannock, Ph.D., whose telephone number is (703) 306-5876. The examiner can normally be reached on Mondays through Thursdays from 8:00 a.m. to 5:30 p.m.

The examiner can also normally be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, Ph.D., can be reached at (703) 308-6564.

Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

MB

June 29, 2003

YVONNE EYLER, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600